Study: **Mapping the practices of scientific (risk assessment) evaluation of active substances used in plant protection products**

The aim of the study is to map regulatory agencies (worldwide) that have assessed hazards and risks of glyphosate, identify regulatory agencies whose scientific conclusions alight and diverge and explain why scientific divergences have occurred (the case of glyphosate scientific evaluation).

The following questions are related to the three main aspects of organizational settings and arrangements within which risk assessments have been conducted:

(1) institutional designs of regulatory agencies (e.g., transparency and independence policies),
(2) procedural mechanisms followed in the scientific activities (e.g., internal working procedures);
(3) technical/scientific aspects of the risk/hazard assessments (e.g., types of evidence used).

List of questions:

Transparency and independence policies:

- How does your organization ensure transparency of its *scientific activities*?

EPA strives for transparency in our scientific analyses. Our science policies, guidance documents, and guidelines have been through peer review and public comments, and are publicly available. Our scientists develop independent, objective evaluations of studies sponsored by pesticide registrants and those available in the open scientific literature. Risk assessments and regulatory decisions are routinely published in a federal docket for public comment and EPA seeks feedback from the public on its scientific methodology and its proposed regulatory decisions. Public comments are reviewed and considered in decision-making. Our scientists routinely give presentations to the public and to other scientific experts. We also frequently meet with stakeholders (including industry, growers, non-governmental organizations, states) on numerous issues pertaining to pesticides. When necessary, EPA also holds publicly accessible Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) meetings to seek feedback and/or technical advice from independent experts. As part of this review process, all relevant documents and studies are accessible in a public docket.

How does your organization safeguard independence of its *scientific outputs*?

EPA performs its own independent evaluation of available data to ensure that pesticides do not pose unreasonable risks to human health or the environment. Often the dataset is composed of hundreds of studies and consists of data from a variety of sources, including extensive human health, product chemistry, environmental fate, and ecotoxicity data from the pesticide producer, other pesticide companies, academia, and published scientific literature. The Agency strives to use high-quality studies to inform risk assessment decisions.

- Were transparency and independence policies followed in the case of glyphosate?

Yes, EPA follows these polices in all pesticide review cases.

- Did the case of glyphosate receive more considerations in terms of independence and transparency in the risk assessment processes/scientific outputs?

EPA routinely completes independent scientific risk assessments and strives to achieve transparency in the risk assessment process and scientific outputs for all pesticide review cases. The same amount of consideration was given to glyphosate; however, EPA provided additional opportunities to solicit technical advice and feedback from independent experts and the public due to the high level of public interest. For instance, the evaluation of the human carcinogenic potential of glyphosate conducted by EPA was presented to the FIFRA SAP. As part of this process, all supporting documentation was publicly available, which included full study reports, the Agency's individual study reviews (data evaluation records, or DERs), and the Agency's issue paper detailing the process and decisions undertaken to reach the conclusions based on a weight-of-evidence approach. The transcript to the glyphosate FIFRA SAP meeting is also available.

- In terms of the processes followed, was the case of glyphosate 'standard', or did your organization invest more time and effort in making procedures more transparent, accessible, etc.

All pesticides, including glyphosate, follow a standard [HYPERLINK "https://www.epa.gov/pesticide-registration/about-pesticide-registration"] and [HYPERLINK "https://www.epa.gov/pesticide-reevaluation/registration-review-process"] process. EPA followed the standard protocol for generating a work plan, requiring data, reviewing open literature data, evaluating registrant submitted studies, completing risk assessments, and soliciting public comment. However, given the high level of public interest in glyphosate's reevaluation and the IARC's conclusion regarding glyphosate's cancer potential, additional steps were used for glyphosate to ensure transparency and scientific quality. Following the IARC decision regarding glyphosate, the EPA Office of Pesticide Program's (OPP) Cancer Assessment Review Committee (CARC) conducted an independent review of the available data for its own reevaluation. Subsequently, a more comprehensive systematic review of studies submitted to the Agency and available in the open literature was performed. All relevant studies were then incorporated into the weight-of-evidence evaluation of the human carcinogenic potential of glyphosate, which was presented to the FIFRA SAP.

EPA will follow the standard protocol when the registration review process reaches the regulatory decision-making phase for glyphosate.

Internal/external control mechanisms (e.g., stakeholder involvement procedures):

- What are the core internal and external control mechanisms that your organization follows to assure accountability of its processes and outputs?
- How does your organization ensure the inclusion of legitimate stakeholders in your scientific work?

- Which stakeholders are most important in your work and why (accountability, transparency, information, efficiency reasons)?
- To which of them are you most responsive?

The pesticide registration and registration review processes are under the broad authority of the following laws. These laws hold EPA accountable for its pesticide processes and outputs:

- [HYPERLINK "https://www.epa.gov/laws-regulations/summary-federal-insecticide-fungicide-and-rodenticide-act"],
- [HYPERLINK "https://www.epa.gov/laws-regulations/summary-federal-food-drug-and-cosmetic-act"],
- [HYPERLINK "https://www.epa.gov/laws-regulations/summary-food-quality-protection-act"] ,
- [HYPERLINK "https://www.gpo.gov/fdsys/pkg/STATUTE-118/pdf/STATUTE-118-Pg3.pdf"], and
- [HYPERLINK "https://www.epa.gov/laws-regulations/summary-endangered-species-act"][HYPERLINK "https://www.epa.gov/laws-regulations/summary-endangered-species-act"]

Public participation is vital to the effective registration and registration review of pesticides. All interested individuals and groups are equally welcome to participate in our multiple opportunities for public comment, which are established in the registration and registration review processes. For more information on how stakeholders can participate see the [HYPERLINK "https://www.epa.gov/pesticide-registration/public-participation-process-registration-actions"] and the [HYPERLINK "https://www.epa.gov/pesticide-reevaluation/opportunities-participate-pesticide-reevaluation"].

Another way we ensure the inclusion of legitimate stakeholders in our scientific and policy decisions is by consulting our federal advisory committees. The [HYPERLINK "https://www.epa.gov/pesticide-advisory-committees-and-regulatory-partners/pesticide-program-dialogue-committee-ppdc"], in particular, is a representative federal advisory committee. Representative members are selected to represent the points of view held by specific organizations, associations, or classes of individuals. In selecting members, EPA will consider candidates from pesticide user, grower and commodity groups; consumer and environmental/public interest groups; farm worker organizations; pesticide industry and trade associations; State, local and Tribal governments; Federal government; academia; the general public; and public health organizations.

Feedback is sought from all avenues and is all valued. EPA routinely receives feedback from:

- Stakeholders that are involved in the manufacturing, handling, and application of pesticides,

- International partners, federal partners, states, and regional authorities who deal with issues involving pesticide policy,
- Scientists who might have expertise in a given area,
- Public interest groups, and
- Members of the general public.

EPA strives to be equally responsive to all feedback, regardless of the stakeholder.

Selection of scientific experts:
The discrepancy between the results presented by regulatory agencies and bodies might be a result of the reliance on scientists with ***different disciplinary backgrounds and experience*** *(e.g., industry versus academic experts).*

- How does your organization select scientific experts for risk assessments?
- What was the background of scientists involved in the risk assessment of glyphosate (Composition of experts in the case of glyphosate)?
- How is the impartiality/independence of scientific experts assured?
- Are there rules / checks for conflict of interest of experts in place?

The glyphosate registration and registration review team is composed of more than two dozen staff with expertise in various disciplines, including toxicology, pharmacology, epidemiology, chemistry, biology, environmental fate, entomology, statistics, risk management, and communications. Like in all executive agencies, EPA employees are subject to the [HYPERLINK "https://www.oge.gov/web/oge.nsf/Employee%20Standards%20of%20Conduct"] issued by the U.S. Office of Government Ethics. These standards provide specific assurances to help guarantee impartiality. EPA employees maintain a high level of ethical conduct to maintain the public trust.

Furthermore, members of FIFRA Scientific Advisory Panel are classified as "[HYPERLINK "https://www.oge.gov/Web/OGE.nsf/Resources/Special+Government+Employees"]" and are similarly subject to [HYPERLINK "https://www.epa.gov/sap/fifra-scientific-advisory-panel-ethics-training"] as required by the office of government ethics to ensure members do not have conflict of interest and can render impartial advice. For glyphosate, panel members were selected based on their knowledge of core expertise needed for the evaluation of the human carcinogenic potential, such as epidemiology, animal bioassays, and genotoxicity.

Data collection:

- What was the data collection process followed in the case of glyphosate?
- How does your organization guarantee a systematic data collection and a review comprehensive of available scientific evidence?

Any company that registers pesticides in the U.S. under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) or seeks a tolerance (maximum legal residue in food) or tolerance

exemption for a pesticide under the Federal Food, Drug, and Cosmetic Act (FFDCA) must conduct a broad suite of studies to meet the requirements of registration. These studies include product chemistry, product performance, human health, environmental fate, ecotoxicity, post-application exposure, spray drift, residue chemistry, and others. [HYPERLINK "https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/master-list-test-guidelines-pesticides-and-toxic"].

FIFRA gives EPA broad authority to establish or modify data requirements and timing for individual pesticide registration actions to achieve statutory and program objectives. Data requirements for pesticide registration actions are found in the Code of Federal Regulations at [HYPERLINK "https://www.ecfr.gov/cgi-bin/text-idx?tpl=/ecfrbrowse/Title40/40cfr158_main_02.tpl"]. These regulations give EPA substantial discretion to make registration decisions on the basis of what we determine to be the most relevant and important data for each action.

The National Academy of Sciences National Research Council (NRC) has encouraged the agency to move toward systematic review processes to enhance the transparency of scientific literature reviews that support chemical-specific risk assessments to inform regulatory decision making. EPA employs "fit for purpose" systematic reviews that rely on standard methods for collecting, evaluating, and integrating the scientific data supporting the agency's decisions. For the evaluation of the human carcinogenic potential of glyphosate, data were collected by searching the open literature and other publicly available sources (e.g., recent internal reviews, evaluations by other organizations). Internal databases were also searched for studies conducted according to Organization for Economic Cooperation and Development (OECD) test guidelines, Office of Chemical Safety and Pollution Prevention (OCSPP) harmonized test guidelines, and other pesticide test guidelines (OPP guidelines). A separate systematic review of the open literature was performed for hazard identification and characterization purposes to identify studies that could potentially impact the human health risk assessment.

Type of evidence:
The discrepancy between the results presented by regulatory agencies and bodies might be a result of the fact that ***risk assessors choose different literature to review****.*

- On which evidence did your organization relied on to draw scientific conclusions in the risk assessment/hazard classification of glyphosate? Why?

EPA's draft human health risk assessment evaluated dietary, residential/non-occupational, aggregate, and occupational exposures. This included an in-depth review of the glyphosate cancer database, including data from epidemiological, animal carcinogenicity, and genotoxicity studies. All the evidence used, and EPA's weight-of-evidence approach is summarized in the human health draft risk assessment and associated documents.

In the draft ecological risk assessment, EPA used the most current risk assessment methods, and completed a comprehensive evaluation of the potential effects of glyphosate exposure on non-

target organisms. Full details on the evidence used as well as the EPA's methods for estimating them, can be found within the ecological risk assessment.

For more information, read the [HYPERLINK "http://www.epa.gov/ingredients-used-pesticide-products/draft-human-health-and-ecological-risk-assessments-glyphosate"].

Scientific approaches used to assess evidence:
The discrepancy between the results presented by regulatory agencies and bodies might be a result of the reliance on ***different methodologies, scientific assessment criteria used to assess available evidence.***

- Which scientific approach(es) did your organization employ to assess scientific evidence? Why?

EPA uses the same standard risk assessment procedure for all pesticides. See[HYPERLINK "https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/overview-risk-assessment-pesticide-program"] Each step in risk assessment (planning, hazard identification, dose-response assessment, exposure assessment, and risk characterization) follows standard criteria. [HYPERLINK "https://www.epa.gov/risk/conducting-human-health-risk-assessment" \l "tab-1"]. Standard [HYPERLINK "https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/guidance-human-health-risk-assessments-pesticides"] for pesticides are followed for every case and are publicly available. Similarly, EPA's standard process for [HYPERLINK "https://www.epa.gov/risk/ecological-risk-assessment"] and standard [HYPERLINK "https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/ecological-guidance-pesticide-risk-assessments"] are publicly available.

The Agency strives to use high-quality studies when evaluating pesticide chemicals and considers a broad set of data during this process. This includes registrant generated studies, typically using OECD test guidelines, required under FIFRA, as well as peer-reviewed scientific journals and other sources, such as other governments and academia. All studies are thoroughly reviewed to ensure appropriate conduct and methodologies are utilized and that sufficient data and details are provided. This ensures that decisions are informed by the best science available.

Studies submitted to the Agency are generally evaluated based on OECD, OCSPP, or OPP test guideline requirements to determine whether studies are acceptable for use in risk assessment and EPA's conclusions about individual studies are summarized in DERs. To evaluate open literature studies, criteria described in the 2012 OPP guidance for considering and using open literature toxicity studies to support human health risk assessment are followed. This guidance assists OPP scientists in their judgement of the scientific quality of open literature publications. More specifically, the document discusses how to screen open literature studies for journal articles/publications that are relevant to risk assessment, how to review potentially useful journal articles/publications and categorize them as to their usefulness in risk assessment, and how the studies may be used in the risk assessment. As with submitted studies, those deemed unacceptable are noted and subsequently excluded from evaluations. EPA uses a weight-of-evidence (WoE) approach when integrating data from multiple sources to take quality, consistency, relevancy, coherence biological plausibility, and uncertainty into account.

Application of WoE analysis is an integrative and interpretive process routinely used by EPA and outlined in its [HYPERLINK "http://www.epa.gov/risk_assessment/guidance.htm"].

Furthermore, all final work products are subjected to multiple levels of internal peer review. This includes reviews of individual studies, hazard and exposure assessments, risk assessments, and any additional supporting documentation.

Opinion questions:

- What is your opinion of the scientific evaluation of glyphosate carried out by the IARC, European Union regulatory authorities (EFSA and ECHA) (applicable only if you are familiar with their scientific evaluations)?
- In your opinion, what are the main reasons of the scientific divergences between the IARC and your organization? How did it affect the final scientific conclusions?
- Whose scientific evaluation of glyphosate would you endorse?

EPA's risk assessment for glyphosate was conducted independently of any other organization and the IARC decision did not influence EPA's conclusions. EPA's cancer classification for glyphosate is based on a weight-of-evidence evaluation in accordance with the Agency's 2005 Guideline for Carcinogen Risk Assessment. The dataset considered by EPA included studies submitted for registration of glyphosate, as well as studies identified in the open literature as part of a systematic review. EPA also incorporated data that were not previously available into its evaluation. IARC only considers data that have been published or accepted for publication in the openly available scientific literature. As a result, IARC only considered a subset of the studies included in EPA's evaluation. EPA also did not use some studies that IARC incorporated into their evaluation because EPA did not believe the studies were appropriate for determining the human carcinogenic potential of glyphosate. For example, genotoxicity studies conducted in non-mammalian species (i.e., worms, fish, reptiles, plants) were excluded from the EPA's evaluation because they were not considered relevant for informing the genotoxic risk in humans.

EPA is confident in its risk assessment and its conclusion that glyphosate is not likely to be carcinogenic to humans. EPA's conclusion is consistent with other countries and regulatory authorities including the Canadian Pest Management Regulatory Agency, Australian Pesticide and Veterinary Medicines Authority, European Food Safety Authority, the European Chemicals Agency, German Federal Institute for Occupational Safety and Health, The Joint FAO/WHO Meeting on Pesticide Residues, the New Zealand Environmental Protection Authority, and Food Safety Commission of Japan.

- Could you indicate which of the following/combination of the following is most relevant in your scientific work:

- Scientific/technical rigorousness
- Following adequate procedures in carrying out your scientific tasks
- Delivering effectively on your mandate
- Acting in the public interest

The agency firmly appreciates the importance of all the elements you listed above, and we believe the regulatory process established for regulation of U.S pesticides is a well-balanced product of those goals.